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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,634	03/27/2000	BARBARA RONIKER	CU-2019-RJS	6230

7590 04/08/2003

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EXAMINER	
JAGOE, DONNA A	
ART UNIT	PAPER NUMBER
1614	24

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/402,634	Applicant(s) RONIKER ET AL.	
	Examin r Donna A. Jagoe	Art Unit 1614	

-- The MAILING DATE f this communication appears on the c ver sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *03 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,15-24,26-32 and 34-68* is/are pending in the application.

4a) Of the above claim(s) *32 and 34-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,15-24,26-31 and 40-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *23* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 13,15-24,26-32 and 34-68 are pending in this application.

Election/Restrictions

Applicant's election with traverse of group I in Paper No. 21 is acknowledged. The traversal is on the ground(s) that both sets of claims contain a unifying thread of requiring a combination of a therapeutically effective amount of a cyclooxygenase-2 (COX-2) inhibitor or a pharmaceutically acceptable salt thereof in combination with a lipid lowering drug. Applicant asserts that this alleges unifying thread shows that the method claims and the composition claims are not separate and distinct. The applicant also asserts that a serious undue burden for the search and examination is simply not waranted. This is not found persuasive because these inventions are distinct/unrelated for the reasons given in paper number 19 and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper. Moreover, because a search of each distinct/unrelated invention would not be coextensive with the other(s), and because each invention will require its own separate patentability analysis, an examination and search of multiple inventions in a single application would constitute a serious undue burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 32 and 34-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 21.

Response to Arguments

Applicant's arguments filed December 3, 2002 have been fully considered but they are not persuasive.

The rejections made in paper numbers 13 and 19 are maintained and are hereby repeated.

1. Applicant cites page 3 of the instant application as defining preventing cardiovascular disorders as preventing the onset of clinically evident cardiovascular disorders, or preventing the onset of pre-clinically evident stage of a cardiovascular disorder and prophylactic treatment of those at risk of developing a cardiovascular disorder. Although the word "prevention" is defined by the instant specification, it is not enabled.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

A. Nature of the Invention: Claim 40 is drawn to a method for preventing onset of a pre-clinically evident cardiovascular disorder in a subject at risk with an

effective amount of a COX-2 inhibitor combined with a lipid-lowering drug. The nature of the invention is extremely complex in that it encompasses the actual prevention of a cardiovascular disorder (i.e. coronary artery disease, aneurysm, arteriosclerosis, atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, angina, coronary plaque inflammation, bacterial induced inflammation, viral induced inflammation and inflammation associated with surgical procedures) such that the subject treated with above compounds does not contract heart disease.

Breath of the Claims: The complex of nature of the claim is greatly exacerbated by breath of the claim. The claims encompass a method for preventing the onset of a pre-clinically evident cardiovascular disorder in a subject at risk, which have potentially many different causes. Each of these defects may or may not be addressed by the administration of the claimed compounds.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds to a subject in order to actually prevent the onset of a pre-clinically evident cardiovascular disorder in a subject at risk is minimal. All of the guidance provided by the specification is directed towards prophylaxis against atherosclerosis specifically.

Working Examples: All of the working examples provided by the specification are directed toward the preventing atherosclerotic lesions in an APOe mouse model. There are no other examples.

State of the Art: While the state of the art is relatively high with regard to **treatment** of the individual conditions that are encompassed by the broad term "cardiovascular disease", the state of the art with regard to prevention of the individual conditions (i.e. coronary artery disease, aneurysm, arteriosclerosis, atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, angina, coronary plaque inflammation, bacterial induced inflammation, viral induced inflammation and inflammation associated with surgical procedures) is very diverse. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **prevent** the onset of a pre-clinically evident aneurysm.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual method for preventing the onset of a pre-clinically evident cardiovascular disorder in a subject at risk with the claimed compounds makes practicing the claimed invention unpredictable in terms of preventing the onset of a pre-clinically evident cardiovascular disease.

The Amount of Experimentation Necessary: In order to practice claimed invention, one of skill in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, a secondary active agent or agents, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for

preventing the onset of a pre-clinically evident cardiovascular disorder in a subject at risk. If unsuccessful, which is likely, given the lack of significant guidance from the specification or prior art with regard to prevention of cardiovascular disease broadly, with any specific composition, one of skill in the art would have to then either envision a modification of the pharmaceutical composition of claim 40, the composition dosage, combination with a secondary active agent, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding preventing the onset of a pre-clinically evident cardiovascular disorder in a subject at risk with a specific composition, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prophylaxis against the development of cardiovascular disease in a subject by administration of one of the claimed active agents.

Therefore, a method for preventing the onset of a pre-clinically evident cardiovascular disorder in a subject at risk comprising administering a COX-2 inhibitor combined with a lipid lowering agent is not considered to be enabled by the instant specification.

B. Nature of the Invention: Claim 49 is drawn to a method for preventing the onset of a clinically evident cardiovascular disorder in a subject at risk with an effective amount of a COX-2 inhibitor combined with a lipid-lowering drug. The nature of the invention is extremely complex in that it encompasses the actual prevention of a cardiovascular disorder (i.e. coronary artery disease, aneurysm, arteriosclerosis, atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, angina, coronary plaque inflammation, bacterial induced inflammation, viral induced inflammation and inflammation associated with surgical procedures) such that the subject treated with above compounds does not contract heart disease.

Breath of the Claims: The complex of nature of the claim is greatly exacerbated by breath of the claim. The claims encompass a method for preventing the onset of a clinically evident cardiovascular disorder in a subject at risk, which have potentially many different causes. Each of these defects may or may not be addressed by the administration of the claimed compounds.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds in order to actually prevent the onset of a clinically evident cardiovascular disorder in a subject at risk is minimal. All of the guidance provided by the specification is directed towards prophylaxis against atherosclerosis specifically.

Working Examples: All of the working examples provided by the specification are directed toward the preventing atherosclerotic lesions in an APOe mouse model. There are no other examples.

State of the Art: While the state of the art is relatively high with regard to **treatment** of the individual conditions that are encompassed by the broad term "cardiovascular disease", the state of the art with regard to prevention of the individual conditions (i.e. coronary artery disease, aneurysm, arteriosclerosis, atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, angina, coronary plaque inflammation, bacterial induced inflammation, viral induced inflammation and inflammation associated with surgical procedures) is very diverse. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **prevent** development of an aneurysm.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to actually preventing the onset of a clinically evident cardiovascular disorder in a subject at risk with the claimed compounds makes practicing the claimed invention unpredictable in terms of preventing the onset of a clinically evident cardiovascular disease.

The Amount of Experimentation Necessary: In order to practice claimed invention, one of skill in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, a secondary active agent or agents, duration of treatment, route of administration, etc. and appropriate

animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for preventing the onset of a clinically evident cardiovascular disorder in a subject at risk. If unsuccessful, which is likely, given the lack of significant guidance from the specification or prior art with regard to prevention of cardiovascular disease broadly, with any specific composition, one of skill in the art would have to then either envision a modification of the pharmaceutical composition of claim 49, the composition dosage, combination with a secondary active agent, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding a method for preventing the onset of a clinically evident cardiovascular disorder in a subject at risk with a specific composition, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prophylaxis against the development of cardiovascular disease in a subject by administration of one of the claimed active agents.

Therefore, a method for preventing the onset of a clinically evident cardiovascular disorder in a subject at risk comprising administering a COX-2 inhibitor combined with a lipid lowering agent is not considered to be enabled by the instant specification.

C. Nature of the Invention: Claim 59 is drawn to a method for treating a subject at risk of developing a cardiovascular disorder with an effective amount of a COX-2 inhibitor combined with a lipid-lowering drug. The nature of the invention is extremely complex in that it encompasses the actual prevention of a cardiovascular disorder (i.e. coronary artery disease, aneurysm, arteriosclerosis, atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, angina, coronary plaque inflammation, bacterial induced inflammation, viral induced inflammation and inflammation associated with surgical procedures) such that the subject treated with above compounds does not contract heart disease.

Breath of the Claims: The complex of nature of the claim is greatly exacerbated by breath of the claim. The claims encompass a method for treating a subject at risk of developing a cardiovascular disorder, which have potentially many different causes. Each of these defects may or may not be addressed by the administration of the claimed compounds.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds in order to actually treat a subject at risk of developing a cardiovascular disorder is minimal. All of the guidance provided by the specification is directed towards prophylaxis against atherosclerosis specifically.

Working Examples: All of the working examples provided by the specification are directed toward the preventing atherosclerotic lesions in an APOe mouse model. There are no other examples.

State of the Art: While the state of the art is relatively high with regard to **treatment** of the individual conditions that are encompassed by the broad term "cardiovascular disease", the state of the art with regard to prevention of the individual conditions (i.e. coronary artery disease, aneurysm, arteriosclerosis, atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, angina, coronary plaque inflammation, bacterial induced inflammation, viral induced inflammation and inflammation associated with surgical procedures) is very diverse. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **prevent** development of an aneurysm.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to actually treating a subject at risk of developing a cardiovascular disorder with the claimed compounds makes practicing the claimed invention unpredictable in terms of preventing the onset of a cardiovascular disorder.

The Amount of Experimentation Necessary: In order to practice claimed invention, one of skill in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, a secondary active agent or agents, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for treating a subject at risk of developing a cardiovascular disorder. If unsuccessful,

which is likely, given the lack of significant guidance from the specification or prior art with regard to prevention of cardiovascular disease broadly, with any specific composition, one of skill in the art would have to then either envision a modification of the pharmaceutical composition of claim 59, the composition dosage, combination with a secondary active agent, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding a method for treating a subject at risk of developing a cardiovascular disorder with a specific composition, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prophylaxis against the development of cardiovascular disease in a subject by administration of one of the claimed active agents.

Therefore, a method for treating a subject at risk of developing a cardiovascular disorder comprising administering a COX-2 inhibitor combined with a lipid lowering agent is not considered to be enabled by the instant specification.

2. Regarding the '797 patent, will not be addressed since each patent application is examined on its own merits and the examiner is presently prosecuting the instant application based on its own merits, not the merits of the '797 patent.

3. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

4. Applicant asserts that the WO 95/15316 teaches that the recited compounds, a particular class of selective COX-2 inhibitors are useful for treatment of inflammation in such diseases as vascular diseases...myocardial ischemia and the like. Applicant asserts that the examiner has made an over-generalization. In response, the examiner turns to the instant specification to shed light on the nature if the instant invention. Page 2, lines 3-9 recite that the role of inflammation in cardiovascular disease is becoming more understood. Ridker et al. teach a possible role of inflammation in cardiovascular disease and J. Boyle teaches the association of plaque rupture and atherosclerotic inflammation. Further, page 2, last full paragraph recites the COX-2 inhibitors of the instant invention useful for the prevention of **inflammation related** cardiovascular disorders. If there is pathway other than treatment of inflammation, used to treat the cardiovascular disorders, it is not described in the instant specification.

5. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, since it is known that anti-inflammatories such as COX-2 inhibitors treat inflammation related vascular diseased and myocardial infarction and since it is known that lipid lowering agent reduce the formation of plaque on blood vessels, it would have been obvious to one of ordinary skill in the art to combine these two agents to treat a vascular disease such as atherosclerosis.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna A. Jagoe whose telephone number is (703) 306-5826. The examiner can normally be reached on 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3230 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Frederick Krass
Primary Examiner
Art Unit 1614

dj
April 6, 2003